REMARKS

With entry of this Amendment, claims 1-21 are pending in the application. By this amendment, claims 4, 5, 14, 17, 18, and 21 have been amended for clarity in accordance with the Office's suggestions. The amendments herein are fully supported by the disclosure, and no new matter has been added to the application. Entry of this amendment is respectfully requested.

Claim Objections

Claim 21 is objected to under 37 CFR 1.75(c), as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. The Office suggests that the subject claim recites an "inherent property" and thereby fails to further limit claims drawn to the method.

Applicants respectfully traverse the stated objection on the basis that the pharmacokinetic term in claim 21 relating to free base plasma concentration is not an inherent aspect that "necessarily flows" from the base claim, at least as established by the Office on evidence of record. Nonetheless, the subject claim has been amended to independent form as suggested by the Office so as to clearly obviate the objection.

Patentability Under 35 USC § 112

Claims 4-5, 7, 14, 17-18, and 21 are rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite.

The Office asserts that the expression "said concentration" in certain claims is indefinite, particularly in terms of which component of the formulation the concentration term is applied to. All subject claims have been amended herein to clarify that the concentration term applies to the "buffer salt" of the formulation.

The Office also contends that the expression "a chemically modified equivalent" or" chemically modified equivalents" in claims 7 and 14 renders the subject claims indefinite. Applicants respectfully traverse. The term "chemically modified equivalent" is believed to adequately convey the metes and bound of the invention to the skilled artisan. As discussed, e.g., at page 7, lines 3-11, the term "scopolamine" is

understood to include "pharmaceutical salts and hydrated forms, as well as chemically modified equivalents" of scopolamine (the reference compound identified, e.g., by reference to the Merck Index; p 7, line 23 to p. 7, line 3). Applicants further teach that a chemically modified equivalent of scopolamine includes "compositions which may have a chemical structure that differs from scopolamine but which functions in a similar manner in the body, such as for example prodrugs, analogs, biologically active fragments and the like." (p. 7, lines 8-11). These terms are readily understood by the artisan of ordinary skill as they relate to the identified reference compound, while the record does not establish that prodrugs, analogs and fragments of scopolamine are in some way not comprehensible in reference to the description. Accordingly, withdrawal of the rejection under 35 USC § 112 as it relates to claims 7 and 14 is earnestly solicited.

The Office further contends that the expression "scopolamine free base plasma concentration is achieved within about 5 minutes" in claim 21 renders the claim indefinite. In particular, the Office argues that the expression must include a numerical concentration value that correlates with the term "scopolamine free base plasma concentration is achieved". Applicants respectfully traverse on the basis that the subject term is made clear by the indicated therapeutic result, which is an acceptable alternative expression to a numeric concentration value. In this regard, the subject claim directly defines the scopolamine free base plasma concentration as a concentration that is effective for "preventing or treating" nausea and/or vomiting "within about five minutes". Clearly, the implicit timing at which such concentration is achieved is between administration and five minutes thereafter. Further in this context, the Office expressly ratifies the use of functional/result expressions to characterize formulations by the reference to Keith (Office Action at p. 4) stating that "the onset of effect is within ten minutes." In reference to Applicants' claim language, the artisan will readily ascertain the metes and bounds of the subject invention by routine clinical assays to determine an "onset of effect" for preventing or treating nausea "within about 5 minutes"—that is in turn directly related to the effective "scopolamine free base plasma concentration" claimed. For these reasons, Applicants respectfully urge that the rejection of claim 21 under 35 USC § 112 be withdrawn.

Patentability Under 35 USC § 103

Claims 1-21 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Keith (W) 83/00286) in view of Osol et al. (Remington's Pharmaceutical Sciences, 15th ed., 1975).

Keith is cited for allegedly disclosing an intranasal formulation comprising scopolamine hydrochloride in a pharmaceutically acceptable carrier, an aqueous solution containing ethanol, which is useful in a method of preventing and/or treating motion sickness such as nausea and/or vomiting. Keith is also relied upon for allegedly teaching that the intranasal formulation therein provides quick relief from motion sickness, with an onset of effect within ten minutes.

The Office concedes that Kieth et al. fails to disclose the employment of polyvinyl alcohol in combination with one or more additional gelling agents or bioadhesives such as alginates, gums, and starches in an intranasal scopolamine formulation and method for treating motion sickness. The Office also recognizes that the primary reference fails to disclose the specific pH values of the instant intranasal formulation, i.e., below about 4 or 3.5. Further, the Office concedes that the Keith reference fails to teach a buffer salt concentration for an intranasal scopolamine formulation as set forth in Applicants' claims of about 200 mM, or 100 mM ,or 50 mM. Nor is it disputed by the Office that Keith et al. fail to disclose employment of the particular salt of scopolamine, hydrobromide and thickening agents and surfactants in the presently claimed formulations. Finally, the Office notes that the primary reference does not disclose an intranasal scopolamine formulation and method that is effective for treating nausea and/or vomiting that is effective within about 5 minutes, as presently claimed.

The Office cites only one secondary reference, Osol et al., in support of the rejection under 35 U.S.C. 103(a). This reference is relied upon for allegedly teaching that "polyvinyl alcohol is a well known pharmaceutically acceptable gelling agent which may be used in combination with one or more additional gelling agents" (e.g., alginates, gums, and starches).

No additional secondary evidence is cited in the record, despite the large number of elements and limitations in Applicants' claims noted by the Office to be lacking in the primary, Keith et al. reference. Even though the cited teachings of Osol et al. are limited to the alleged utility of polyvinyl alcohol and other "gelling agents or bioadhesives", and despite the noted deficiencies of Keith et al., the Office renders a blanket conclusion regarding obviousness, as follows:

> It would have been obvious to a person of ordinary skill in the art at the time of the invention to employ polyvinyl alcohol in combination with one or more additional gelling agents or bioadhesives such as alginates, gums, and starches in the instant intranasal formulation and method for the treatment of nausea and/or vomiting associated with motion sickness, and to employ the particular salt of scopolamine, hydrobromide, and to further employ thickening agents and surfactants in the formulation herein, and to optimize the pH of the instant intranasal formulation to below about 4 or 3.5 and the concentration of the buffer salt in the instant intranasal formulation to below about 200 mM or 100 mM or 50 mM. (Office Action at pp. 4-5).

Notably, no references are provided by the Office that relate to the use of scopolamine salts, thickening agents or surfactants, much less that teach or suggest the combination of such agents as presently claimed. Absolutely no specific teachings are referenced that address a problem or direction that would suggest and guide how to "optimize the pH", or adjust the buffer salt concentration to "below about 200 mM or 100 mM or 50 mM." The presumed "motivation" to modify the teachings of Keith in this regard is therefore wholly unsupported by the record.

Concerning the use of polyvinyl alcohol, gelling agents, bioadhesives, scopolamine salts, thickening agents, and surfactants, the Office provides no direct suggestion or "compelling motivation" as required by Section 103 to modify the Keith reference to incorporate any of these presently claimed features. In this regard, the Office cites the Examples of Kieth that teach simple, aqueous and alcohol formulations of unmodified scopolamine. According to the Office's own interpretation, these simple compositions are allegedly highly effective for rapidly treating motion sickness and

nausea. By virtue of this supposed effectiveness, no suggestion is apparent in the primary reference, or in the secondary, Osol et al. reference, to modify the simple aqueous/alcohol scopolamine formulation of Keith in the manner disclosed by Applicants. On the contrary, because the cited references fail to disclose any "apparent disadvantage" to the prior art formulation, they clearly fail to suggest the desirability of any of the particular modifications proposed by the Office based on a hindsight analysis of Applicants' invention (see, e.g., Winter International Realty Corp. v. Wang, 53 USPQ2d 1580, 1587 (CAFC, 2000).

The Office further contends that "one of ordinary skill in the art would have been motivated to optimize the pH of the instant intranasal formulation to below about 4 or 3.5, and to optimize the concentration of the buffer salt in the instant intranasal formulation to below about 200 mM or 100 mM or 50 mM." Again, no documentary evidence or specific, scientific reasoning is provided by the Office in support of these contentions. On the contrary, the primary reference must be interpreted as "teaching away" from any need to modify or optimize the simple, aqueous/alcohol scopolamine formulations described in Keith—based on the Office's own interpretation that the formulations of Keith are highly effective for their intended purpose.

In this regard, Applicants note that the formulation of Keith et al. is disclosed as a simple aerosol spray made by dissolving 1 mg of scopolamine in 99.9 ml of a stock solution of 20% ethanol in water. No disclosure is provided concerning the desirability of a buffer salt, much less a particular buffer salt concentration. In the Examples following this disclosure a number of subject cases reportedly demonstrated "quick action", "sustained relief" and "no side effects" for the formulation. Certainly, this disclosure is inconsistent with a "compelling" suggestion or motivation to modify the Keith formulation as proposed by the Office.

To properly interpret the present facts, the Office's attention is respectfully directed to the CCPA's decision in In re Taborsky (183, USPQ 50, 55 (1974)). There, the Federal Circuit's predecessor court clarified the standards for determining obviousness, as follows:

> In determining the propriety of the Patent Office case for *prima facie* obviousness, it is necessary to ascertain whether the prior art teachings would appear to be sufficient to one of ordinary skill in the art to suggest making the proposed substitution or other modification.
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> ***
>
> [W]hat on this record--other than abstract, theoretical or academic considerations--would lead one of ordinary skill to change the structure of the reference compounds to obtain the claimed compounds?

In the instant case, nothing in the record suggests modifying the Keith et al. scopolamine formulation by adding a buffer salt in the particular concentration range claimed by Applicant, or by adjusting the pH to the values set forth in the claims presented for review. Accordingly, no *prima facie* case of obvious has been made, and the rejection of claims 1-21 under 35 U.S.C. 103(a) as allegedly unpatentable over Keith in view of Osol et al. is believed to be overcome.

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is therefore respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206.332.1380.

Date: November 30, 2001

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. An intranasal formulation comprising scopolamine in a pharmaceutically acceptable carrier at a pH below about 4.0 and a buffer salt concentration below about 200 mM, said carrier incorporating polyvinyl alcohol.

2. An intranasal formulation as in claim 1, wherein said carrier is a pharmaceutically acceptable gel.

3. An intranasal formulation as in claim 1, wherein said polyvinyl alcohol is combined with one or more additional gelling agents or bio-adhesives selected from the group including alginates, gums, starches, polyacrylates, dextrans, chitosans and mixtures thereof.

4. (Amended) An intranasal formulation as in claim 1, wherein said buffer salt concentration is at or below about 100 mM.

5. (Amended) An intranasal formulation as in claim 1, wherein said buffer salt concentration is at or below about 50 mM.

6. An intranasal formulation as in claim 1, wherein said pH is about 3.5.

7. An intranasal formulation as in claim 1, wherein said scopolamine is provided as a chemically modified equivalent or pharmaceutically acceptable salt thereof.

8. An intranasal formulation as in claim 7, wherein said scopolamine is provided as scopolamine hydrobromide.

9. An intranasal formulation for preventing anchor treating nausea anchor vomiting described in claim 1.

10. An intranasal formulation as in claim 1 further including buffering agents, thickening agents, tolerance enhancers, surfactants, excipients, preservatives and combinations thereof.

11. An intranasal gel formulation for preventing and/or treating motion sickness comprising scopolamine hydrobromide in a gel solution at or below a pH at about 3.5 and a buffer salt concentration at or below about 100 mM, said gel solution incorporating polyvinyl alcohol as a gelling agent.

12. An intranasal formulation as in claim 11, wherein said gel solution further includes gelling agents and/or bio-adhesives selected from the group including alginates, gums, starches, polyacrylates, dextrans, chitosans and mixtures thereof.

13. An intranasal gel formulation as in claim 11 further including buffering agents, thickening agents, tolerance enhancers, surfactants, excipients, preservatives and combinations thereof.

14. (Amended) A method of preventing and/or treating nausea and/or vomiting comprising administering intranasally to a mammal an effective amount of scopolamine, or a chemically modified [equivalents and pharmaceutical salts] equivalent or pharmaceutical salt thereof in a pharmaceutically acceptable carrier at a pH below about 4.0 and a buffer salt concentration below about 200 mM, said carrier incorporating polyvinyl alcohol.

15. A method as in claim 14, wherein said carrier further includes gelling agents and/or bio-adhesives selected from the group including alginates, gums, starches, polyacrylates, dextrans, chitosans and mixtures thereof.

16. A method as in claim 14, wherein said carrier is a gel for intranasal administration.

17. (Amended) A method as in claim 14, wherein said buffer salt concentration is at or below about 100 mM.

18. (Amended) A method as in claim 14, wherein said buffer salt concentration is at or below about 50 mM.

19. A method as in claim 14, wherein said pH is about 3.5.

20. A method as in claim 14, wherein said scopolamine is provided as scopolamine hydrobromide.

21. (Amended) A method [as in claim 14] of preventing and/or treating nausea and/or vomiting comprising administering intranasally to a mammalian subject an effective amount of scopolamine, or a chemically modified equivalent or pharmaceutical salt thereof in a pharmaceutically acceptable carrier at a pH below about 4.0 and a buffer salt concentration below about 200 mM, said carrier incorporating polyvinyl alcohol, wherein a nausea and/or vomiting preventing or treating scopolamine free base plasma concentration for said subject is achieved within about 5 minutes.